REMARKS

Claims 1, 3 – 5 and 7 – 20, as amended, and new claims 21 – 24 are pending in the application. Claims 2 and 6 were previously canceled without prejudice. The amendments to claims 1, 3 – 5, 7, 8, and 14 were submitted to correct a lack of antecedent basis for the term "compound." Applicants substitute the phrase "ospemifene or a pharmaceutically acceptable salt thereof" for the term "compound." New claims 21 – 24 are directed to methods of inhibiting urogentital atrophy. Support for new claims 21 – 24 can be found at in the specification at paragraph [0024]. Therefore, no new matter is added.

Reconsideration and re-examination of this application in view of the following remarks is hereby respectfully requested.

I. REJECTION UNDER 35 U.S.C. §103(a)

Claims 1, 3 – 5 and 7 – 20 stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Anttila in view of DeGregorio et al. (US 5,750,576) and Huebner et al. (US 6,387,920) as evidence by Kangas (1990). In support of his argument that the pending claims are obvious, the Examiner argues on pages 5-7 of the Final Rejection:

- Antilla discloses administering 60 mg/day of "a metabolite [of] toremifene" to healthy male volunteers during or after a meal;
- the oral administration of toremifene "would reasonably inherently cause secretion of bile acids, and inherently enhance bioavailability of toremifene;"
- toremifene is structurally similar to ospemifene;
- administration of a drug that metabolizes to the active form in vivo is the same as administering the metabolite;
- DeGregorio teaches 5-100 mg/day oral administration of ospemifene to treat osteoporosis; and
- Huebner et al. disclose the use of estrogen receptor modulators in combination with toremifene to treat osteoporosis, skin or vaginal atrophy and it would be obvious to substitute one estrogen receptor modulator for another.

In applicant's prior Amendment dated April 30, 2010, applicant submitted the Lammintausta declaration under 37 C.F.R. §1.132 to contest several of the technical assumptions made by the Examiner in support of the obviousness rejection. For example, the Lammintausta declaration establishes the following facts.

- Antilla does not disclose the administration of a metabolite of toremifene (see Lammintausta declaration ¶ 19).
- Administration of a drug that metabolizes to the active form in vivo is *not* the same as administering the metabolite unless the parent drug itself is inactive (see Lammintausta declaration ¶ 20).
- Toremifene is active and dominates the clinical tissue-specific profile in comparison with its metabolites. Ospemifene is a minor metabolite of toremifene and does not contribute to the effect of toremifene and its main metabolite desmethyltoremifene as breast cancer compounds (see Lammintausta declaration ¶¶ 20-21).
- Although ospemifene and toremifene are structural relatives, their pharmacokinetics are significantly different in regard to their elimination rates and metabolism (see Lammintausta declaration ¶ 22).
- It is incorrect to assert that food would inherently enhance the bioavailability of toremifene. Antilla teaches that toremifene "works equally well with or without administration of food" (see Lammintausta declaration ¶ 23).
- The DeGregorio reference does not teach the administration of a drug with a meal nor does it teach the use of ospemifene to treat either vaginal atrophy or symptoms thereof (see Lammintausta declaration ¶ 24).
- Huebner et al. relate to structurally unrelated isoxazole estrogen receptor agonist and antagonist compounds. The isoxazoles show divergent activities in that some are estrogen agonists and some are estrogen antagonists (see Lammintausta declaration ¶ 25).
- Each SERM has the potential to induce an absolutely unique set of pharmacological effects. Further, there is no generalized theory for SERMs such that upon seeing a dose dependent response as to a positive effect, one would

not know whether a comparable dose dependent response as to negative effects would occur (see Lammintausta declaration ¶¶ 20-21).

- Applicant unexpectedly found a significant 2-3 fold improvement of ospemifene bioavailability when administered with food (see Lammintausta declaration ¶ 28).

By maintaining the rejection under the same reasoning the Examiner ignores several of the facts established by the Lammintausta declaration. The Lammintausta declaration demonstrates that one of ordinary skill in the art would not have a reasonable expectation that administering ospemifene with food according to the claims would significantly increase bioavailability. In practical terms, higher dosages of ospemifene would be required for the same therapeutic effect if administered without food. Therefore, applicant maintains that Claims 1, 3-5 and 7-13 are nonobvious and respectfully requests that the rejection under 35 U.S.C. 103(a) over Anttila in view of DeGregorio et al. (US 5,750,576) and Huebner et al. (US 6,387,920) as evidence by Kangas (1990) be withdrawn.

II. FIRST REJECTION FOR OBVIOUSNESS-TYPE DOUBLE PATENTING

Claims 1, 3-5 and 7-20 stand rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 5-6, 10 and 13-28 of U.S. Patent Application No. 11/201,098 (US 2005/0272825). The Examiner argues that whether or not the instant claims are directed to bioavailability there is no distinguishing step that indicates once the drug is administered it would not treat urinary symptoms. Applicant respectfully disagrees. As pointed out in a prior office action, the Examiner has already taken the position that "food can be an active agent as it comprises nutrients for the functioning of the body." Office Action dated April 30, 2008, page 6. Applicant points out that one distinguishing step between the claimed invention and the prior art is the administration of ospemifene after prompting a bile-rich environment in the gastrointestinal tract.

The Examiner argues that because Vasu teaches that drugs are known to be commonly administered with food or without food that this would motivate one to combine the prior art references to achieve the claimed invention. Applicant points out that in order for there to be motivation to combine references in a way to suggest a claimed invention, one of ordinary skill in the art must have a reasonable expectation of

success. One of ordinary skill in the art had no expectation that administering ospemifene slightly before, during or after food intake would have such a dramatic positive effect on the oral bioavailability of the drug. Rather, the prior art actually taught away from the invention as we have specifically set forth in prior replies. Further, applicant reminds the Examiner that "[p]atentability shall not be negatived by the manner in which the invention was made." 35 U.S.C. 103(a), last sentence.

Applicant respectfully submits that claims 1, 3-5 and 7-20 should not be rejected for obviousness-type double patenting over the '098 patent application, in view of the teaching away of Anttila, and the unexpected results in disclosed in the specification. Therefore, Applicant respectfully requests that the obviousness-type double patenting rejection of claims 1, 3-5 and 7-20 over US Application No. 11/201,098 be withdrawn.

III. SECOND REJECTION FOR OBVIOUSNESS-TYPE DOUBLE PATENTING

Claims 1, 3-5 and 7-20 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 of U.S. Patent No. 6,984,665 ("the '665 patent"). The Examiner argues that as evident by Vasu, drugs are known to be administered with food. In reply, applicant agrees that it is known that drugs are administered with food, but one would not have known the effect of co-administering food under the claimed conditions. Food can have positive, negative, or neutral effects on the bioavailability of drugs and the effects and extent of those effects cannot typically be known until empirically tested as applicants have done here. For the reasons set forth above in response to the first rejection of the claims for obviousness-type double patenting, applicant similarly maintains that claims 1, 3-5 and 7-20 should not be rejected for obviousness-type double patenting, in view of the teaching away of Anttila, and the unexpected results in disclosed in the specification. Therefore, Applicant respectfully requests that the obviousness-type double patenting rejection of claims 1, 3-5 and 7-20 over the '665 patent be withdrawn.

IV. THIRD REJECTION FOR OBVIOUSNESS-TYPE DOUBLE PATENTING

Claims 1, 3-5 and 7-20 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 of U.S. Patent No. 6,245,819 ("the '819 patent").

The Examiner cites the '819 patent in rejection but cites portions of the '665 patent in rejection. While there are many passages of the '819 patent that are contained in the '665 patent, the Examiner cites portions of the '665 patent that are not contained in the '819 patent. As argued above, the '665 patent is deficient in teaching or suggesting the claimed invention. In the same way, the '819 patent is deficient as it is silent regarding improving bioavailability of ospemifene by co-administration of food. For the reasons set forth above in response to the first rejection of the claims for obviousness-type double patenting, applicant similarly maintains that claims 1, 3-5 and 7-20 should not be rejected for obviousness-type double patenting, in view of the teaching away of Anttila, and the unexpected results in disclosed in the specification. Therefore, Applicant respectfully requests that the obviousness-type double patenting rejection of claims 1, 3-5 and 7-20 over the '819 patent be withdrawn.

In view of the above amendments and remarks, it is submitted that the claims are in condition for immediate allowance. The Examiner is invited to contact the undersigned attorneys for the Applicant via telephone if such communication would expedite this application.

Respectfully submitted,

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